Reviewed by: Linda L. Taylor, Ph.D. Linda Lee Taylor 6/3/87
Section III, Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D. M. van Gemert 6/4/87
Section III, Tox. Branch (TS-769C)

DATA EVALUATION REPORT

STUDY TYPE: 21-Day Repeat Dermal Application in Rats TOX. CHEM. NO.: 838B

MRID NO.: 401413-06

TEST MATERIAL: 2,3,5,6-tetrafluoro-4-methylbenzyl (1RS) cis-3-(Z-2-chloro-3,3,3-trifluorlprop-1-enyl)-2,2-dimethlycyclopropanecarboxylate

SYNONYMS: PP993; tefluthrin 12492

STUDY NUMBER: CTL Study No. LR0511

SPONSOR: ICI Americas Inc.

TESTING FACILITY: ICI Central Toxicology Laboratory

TITLE OF REPORT: PP993: Subacute Dermal Toxicity to Rats

AUTHORS: J. Southwood

REPORT ISSUED: July 23, 1985

CONCLUSIONS: PP993 showed neurotoxic effects that were manifested in front paw flicking, tremors, and abnormal gait. Triglyceride levels were decreased in both sexes at the mid- and high-dose levels. In males, there was a dose-related, statistically significant, decrease in both the white blood cell and lymphocyte counts at all dose levels. In females, the decrease in magnesium levels was also dose-related and statistically significant at all dose levels.

The NOEL for neurotoxic effects in males is 5 mg/kg; for females, 1 mg/kg. For clinical effects, no NOEL was determined for either sex.

Classification: Core supplementary, pending submission of (1) clarification data regarding the clinical findings; (2) the means + standard deviations for the high-dose female body weights for Days 1-17 in Table 4 of the supplement; and (3) an explanation of why the skin of all animals was not examined.

QUALITY ASSURANCE: A quality assurance statement was provided.

A. MATERIALS:

1. Test compound: 2,3,5,6-tetrafluoro-4-methylbenzyl (1RS) cis-3-(Z-2-chloro-3,3,3-trifluorlprop-1-enyl)-2,2-dimethlycyclopropanecarboxylate; Description: straw-colored liquid; Batch No. P14 D2978/69; Purity: 90.4%.

2. Test animal: Species: Rat; Strain: Alderley Park SPF albino; Age: 7-10 weeks; Weight: 250-307 grams (males), 185-225 grams (females); Source: Animal Breeding Unit, Pharmaceuticals Division, Alderley Park, UK.

B. STUDY DESIGN:

Methodology

Rats were assigned randomly to one of four (three test and one control) groups of ten males and 10 females. The nominal dose levels were 1, 5, and 50 mg PP993/kg body weight (applied as a solution in polyethylene glycol 300, which was also used as the control). The dorsal-lumbar region of each animal was clipped at least 18 hours, but no more than 24 hours, before the first application of the test material. The vehicle control and test material were dermally applied (21 six-hour applications), with an 18-hour period between each application. During this 18-hour period, each rat was fitted with a plastic collar to prevent grooming and any oral ingestion of the test material. The exposure area was approximately 100 mm X 50 mm. A standard volume of 2 ml/kg of the dosing preparations was applied to each of the test animals and, differences in dose were achieved by varying the concentration of the preparations. The test material was kept in contact with the skin for at least six hours after application by means of an occlusive dressing. At the end of the 6-hour period the dressing was removed, the site of application cleansed free of the test substance, and the test site was dried.

Observations

All rats were examined daily, prior to dosing and after decontamination, for signs of toxicity and dermal irritation at the site of application. Body weights were recorded daily to assess the amount of test substance to be applied, and food consumption (per cage over a 24-hour period) was measured once a week. Animals had free access to food (Porton Combined diet) and water.

Clinical Pathology

Blood was collected from each animal at necropsy for hematology and biochemical analyses. The animals were sacrificed one day after the final dose; no information was provided as to whether the animals were fasted prior to sacrifice. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)	X	Leukocyte differential count
X	Hemoglobin (HGB)	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpuscular HGB conc.(MCHC)
X	Erythrocyte count (RBC)	X	Mean corpuscular volume (MCV)
X	Platelet count		Nucleated red blood cell count
X	Prothrombin time	X	Kaolin-cephalin time

b. Clinical Chemistry

	Electrolytes:		Other:
X	Calcium	X	Albumin
	Chloride		Blood creatinine
X	Magnesium	X	Blood urea nitrogen
X	Phosphorous	X	Cholesterol
X	Potassium		Globulins
X	Sodium	X	Glucose
	Enzymes		Total Bilirubin
X	Alkaline phosphatase	X	Total Protein
	Cholinesterase	X	Triglycerides
	Creatinine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase		
X	Serum alanine aminotransferase (also SGPT)		
X	Serum aspartate aminotransferase (also SGOT)		
	gamma glutamyl transferase		
	glutamate dehydrogenase		

Gross Pathology

At necropsy, the CHECKED (X) parameters were collected for histological examination.

	Digestive system		Cardiovasc./Hemat.		Neurologic
	Tongue		Aorta	X	Brain*
X	Salivary glands	X	Heart	X	Periph. nerve (sciatic)*
	Esophagus		Bone marrow	X	Spinal cord*
	Stomach	X	Lymph nodes (cervical)	X	Pituitary
	Duodenum	X	Spleen		Eyes (optic n.)
	Jejunum	X	Thymus		Glandular
	Ileum		Urogenital	X	Adrenals
	Cecum	X	Kidneys*		Lacrimal gland
	Colon	X	Urinary bladder	X	Mammary gland
	Rectum	X	Testes		Parathyroids
X	Liver*	X	Epididymides		Thyroids
	Gall bladder	X	Prostate		Other
	Pancreas	X	Seminal vesicle	X	Bone (femur)
	Respiratory	X	Ovaries		Skeletal muscle
	Trachea	X	Uterus	X	Skin (test site)*
X	Lung	X	Cervix	X	All gross lesions* and masses
	Nose	X	Vagina		
	Pharynx				
	Larynx				

* processed to wax blocks, sectioned, and stained (H&E)-all animals

The liver, kidneys, brain, and testes (combined, the epididymides were removed from the testes) were weighed at necropsy.

Statistics

Data were analyzed separately for each sex using a two-sided Student's t-test.

C. RESULTS

Survival

Two animals (one high-dose male on day 6 and one mid-dose female apparently on day 15) died during the study. The cause of the male death could not be determined; the female was sacrificed because malocclusion prevented normal feeding.

Clinical Signs and Dermal Irritation

A number of dose-dependent, compound-related systemic effects were reported in the rats administered 21 daily dermal doses of PP993 (see Tables 1 and 2). The type of neurological effects observed included: flicking of the front paws, tremors or shaking, abnormal gait (tip-toe, splayed gait), and downward curvature of the spine (see Table 3).

Comment- In the individual data supplement provided, Table 1 lists the individual clinical findings per day for each animal. It is not clear to this reviewer what some of the findings were, although Appendix 1 supposedly gives the meaning of the acronyms used to describe the findings. For example, for the term: upward curve of the spine, a listing of NS is given for control male # 3 on Days 8 and 13, SS on Days 3, 4, and 14. Appendix defines N as "absent/no abnormalities detected at post mortem"; and S as "slight". No separate definition is given for NS or SS. Another example is seen for the term chromodacryorrhea. Animal # 17 (female control) has a B listed for Day 1 (Appendix defines as "both"), BR (Appendix defines as "breathing rate") for Day 2, BB for Day 8, BN for Day 9, and PN for Day 16. These latter three acronyms are not defined as such in Appendix 1.

Body Weight and Food Consumption

The high-dose animals showed an initial delay in body-weight gain, but by the end of the study, the body weight of all affected animals was reported as comparable to control.

	Percent of Control		
DAY OF WEIGHING	1 mg/kg	5 mg/kg	50 mg/kg
		MALES	
1	99.1	100.6	98.7
8	94.9	99.1	89.7
15	96.6	102.2	95.6
22	97.2	101.6	98.5

		FEMALES	
1	102.3	99.6	100.5
8	99.8	98.8	96.5
15	100.5	97.0	98.2
22	99.7	97.4	100.0

The low-dose males gained very little weight during the first week of the study and they remained lighter than the other males for the duration of the exposure period. This effect was not observed in the females of this group. Note-In the individual data, no mean and standard deviation is provided for the high-dose female body weights for Days 1-17 in Table 4 of supplement.

There was no evidence of any treatment-related effect on food consumption but the low-dose males displayed a statistically significant reduction at Day 13. This decrease does not correspond with the earlier small weight gain in this group between days 1 and 8.

Hematology and Biochemical Analysis

There was a reduction in hemoglobin, hematocrit, white blood cell count, and lymphocyte count observed in the high-dose males, while the females of this dose group displayed comparable decreases in hemoglobin and hematocrit and a decrease in red blood cell count. A decrease in lymphocyte count was also observed at the two other male dose levels, and the decrease was dose-related. The mid- and low-dose males also displayed decreases in white blood cell counts (see Tables 11 and 12).

There was a dose-related decrease in triglycerides in both sexes at the mid- and high-dose levels. Males also displayed dose-related decreases in albumin and total protein and increases (dose-related) in potassium values at these dose levels. Females of the low- and high-dose groups displayed decreases in total protein. Calcium was increased and phosphorus was decreased in the high-dose females, and there was a dose-related decrease in magnesium values at all dose levels in the female (see Tables 9 and 10). Note: Parameters not measured were: Chloride, blood creatinine, and total bilirubin.

Gross Pathology

The relative kidney weight was decreased in the mid- and high-dose males ($p<0.05$) and the absolute kidney weight was decreased in the low-dose males. The high-dose males also displayed a reduced absolute liver weight ($p<0.05$) and a reduced relative liver weight ($p<0.01$). No changes in organ weight were recorded in the females.

Histology

It is reported that the post mortem and histological examinations revealed no evidence of any treatment-related effect. With regard to the skin (test site), focal scab formation with minimal dermal edema, minimal acanthosis,

focal ulceration and focal minimal hyperkeratosis was the only finding reported for this tissue, and it occurred in 1 out of 8 high-dose females.

Note-No explanation was provided as to why the skin of all ten males and 10 females per group were not examined.

In the kidney, minimal microlithiasis at the corticomedullary junction was observed in 7/10 control, 8/10 low-dose, 7 mid-dose, and 10/10 high-dose females.

D. DISCUSSION

A neurotoxic effect was observed at the high-dose level in both sexes. Front paw flicking and tremors were said to reflect central nervous system toxicity, while the abnormal gait effects were indicative of neuromuscular dysfunction. These neurotoxic effects were said to be transient, and no evidence of a histological change in sciatic nerve, spinal cord, or brain was reported.

The occurrance of slight abnormal gait in two mid-dose males was considered by the author to be comparable to control, and the 5 mg/kg dose was said to be the NOEL for this effect in males.

In the females at the 5 mg/kg dose level, the slight gait effects observed were noted more frequently than in the males of this group, but were markedly less frequent than in the high-dose females. The 1 mg/kg dose level was said to be the NOEL for this effect in females.

The author did not consider the body weight reduction in the high-dose group to be an indication of a toxic effect, but rather an adaptive phenomenon. Although there was no comparable reduction in food consumption, the author stated that there was some indication of a change in metabolism and a possible mild hepatic effect. This was manifested in the decreased plasma triglyceride concentration, which suggested an increase in hepatic lipid metabolism. Since cholesterol levels remained normal, the lower triglyceride levels were not considered an indication of a general hypolipidemia. Another effect suggesting decreased liver synthesis was the decrease in plasma protein and albumin (seen in males only). Since no histopathological changes were observed, the author concluded that PP993 had a slight hepatic effect of equivocal toxicological significance.

In males, there was a dose-related, statistically significant, decrease in both the white blood cell and lymphocyte counts at all dose levels. In females, the decrease in magnesium levels was also dose-related and statistically significant at all dose levels. For clinical signs, no NOEL was determined for either sex.

Pages 7-23 Access to FIFRA Registration Data is restricted under FIFRA section 10(g)

13544

R057377

Chemical:	**Tefluthrin**
PC Code:	**128912**
HED File Code	**13000 Tox Reviews**
Memo Date:	**06/04/87 12:00:00 AM**
File ID:	**00000000**
Accession Number:	**412-04-0140**

HED Records Reference Center
04/01/2004